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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NK CELLS ACTIVATING RECEPTORS AND THEIR THERAPEUTIC AND DIAGNOSTIC USES

(57) Abstract: The invention relates to a targeting complex, capable of targeting an active substance to a target cell, said complex comprising: a target recognition segment comprising one of Nkp46, Nkp30, Nkp44 or a functional fragment thereof; and an active segment comprising an active substance such as cytotoxic moiety; an imaging moiety; or an Ig fragment. The targeting complex of the invention serves as a therapeutic agents for the treatment of pathologies associated with viral infections or cancer and for the imaging and monitoring of cancer.



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INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C12N15/62 C12N15/12 C07K14/705 C07K16/18 A61K38/17
 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, SEQUENCE SEARCH, MEDLINE, BIOTECHNOLOGY ABS, EMBASE, PASCAL, WPI Data, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PESSINO A ET AL: "MOLECULAR CLONING OF NKP46: A NOVEL MEMBER OF THE IMMUNOGLOBULIN SUPERFAMILY INVOLVED IN TRIGGERING OF NATURAL CYTOTOXICITY" JOURNAL OF EXPERIMENTAL MEDICINE, TOKYO, JP, vol. 188, no. 5, 7 September 1998 (1998-09-07), pages 953-960, XP000953037 ISSN: 0022-1007 cited in the application	31, 32, 35, 36
Y	abstract; figure 2	1-3, 5, 6, 8-21, 23-25, 27-30, 37-39, 41-45, 47-53, 55, 56,
-/--		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

11 June 2002

Date of mailing of the international search report

13. 08. 2002

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IL 01/00664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>page 954, left-hand column, paragraph 3 ---</p> <p>CANTONI C ET AL: "Nkp44, a triggering receptor involved in tumor cell lysis by activated human natural killer cells, is a novel member of the immunoglobulin superfamily" JOURNAL OF EXPERIMENTAL MEDICINE, TOKYO, JP, vol. 189, no. 5, 1 March 1999 (1999-03-01), pages 787-795, XP002167574 ISSN: 0022-1007 cited in the application abstract; figure 3</p>	<p>58-60</p> <p>31,35,36</p>
Y	<p>page 788, left-hand column, paragraph 6 ---</p> <p>MANDELBOIM OFER ET AL: "Human CD16 as a lysis receptor mediating direct natural killer cell cytotoxicity." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 10, 11 May 1999 (1999-05-11), pages 5640-5644, XP002191492 May 11, 1999 ISSN: 0027-8424 cited in the application abstract page 5640, right-hand column, paragraph 3 ---</p>	<p>1,5,6, 8-18, 23-25, 28,30, 37-39, 44,45, 47-51, 55,56, 58-60</p>
Y	<p>DATABASE EMBL [Online] 22 September 1998 (1998-09-22) BIASSONI R.: " Homo sapiens mRNA for NK receptor (Nkp46), isoform b" retrieved from EBI Database accession no. AJ006121 XP002191532 abstract --- -/--</p>	<p>3,21,29, 42,52,53</p>

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IL 01/00664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PENDE D ET AL: "Identification and molecular characterization of Nkp30, a novel triggering receptor involved in natural cytotoxicity mediated by human natural killer cells"</p> <p>JOURNAL OF EXPERIMENTAL MEDICINE, TOKYO, JP,</p> <p>vol. 190, no. 10,</p> <p>15 November 1999 (1999-11-15), pages 1505-1516, XP002167575</p> <p>ISSN: 0022-1007</p> <p>abstract; figure 7</p> <p>---</p>	<p>1,8-18,</p> <p>37-39,</p> <p>51,58-60</p>
X	<p>MAZANEC MARY B ET AL: "Intracellular neutralization of influenza virus by immunoglobulin A anti-hemagglutinin monoclonal antibodies."</p> <p>JOURNAL OF VIROLOGY,</p> <p>vol. 69, no. 2, 1995, pages 1339-1343, XP002201819</p> <p>ISSN: 0022-538X</p> <p>abstract</p> <p>page 1339, right-hand column, line 26 - line 30</p> <p>---</p>	<p>33-36</p>
X	<p>MAZANEC M B ET AL: "INTRACELLULAR NEUTRALIZATION OF VIRUS BY IMMUNOGLOBULIN A ANTIBODIES"</p> <p>PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES,</p> <p>vol. 89, no. 15, 1992, pages 6901-6905, XP002201820</p> <p>1992</p> <p>ISSN: 0027-8424</p> <p>abstract</p> <p>---</p>	<p>33-36</p>
Y	<p>WO 96 36720 A (SQUIBB BRISTOL MYERS CO)</p> <p>21 November 1996 (1996-11-21)</p> <p>claims 1-4; figure 7; example 1</p> <p>---</p>	<p>8,21,25,</p> <p>27,28,47</p>
Y	<p>WO 99 23867 A (BIOGEN INC ;BROWNING JEFFREY (US))</p> <p>20 May 1999 (1999-05-20)</p> <p>abstract; claim 19; figure 5</p> <p>---</p>	<p>1,10-12</p>
A	<p>WO 96 25953 A (GEN HOSPITAL CORP)</p> <p>29 August 1996 (1996-08-29)</p> <p>examples 7,9</p> <p>---</p> <p>--/</p>	<p>1-3,</p> <p>8-21,27,</p> <p>29,31,</p> <p>33-39,</p> <p>41-43,</p> <p>47-51,</p> <p>53,58-60</p>

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 01/00664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 26265 A (GEN HOSPITAL CORP) 29 August 1996 (1996-08-29) abstract; claims 1-40; figure 1 ---	1-3, 8-21,27, 29,31, 33-39, 41-43, 47-51, 53,58-60
A	WO 95 09011 A (UNIV PENNSYLVANIA) 6 April 1995 (1995-04-06) abstract; example 5 ---	1-3, 8-21,27, 29,31, 33-39, 41-43, 47-51, 53,58-60
A	DATABASE EMBL [Online] 22 September 1998 (1998-09-22) BIASSONI R.: "Homo sapiens mRNA for NK receptor (NKp46) isoform c" retrieved from EBI Database accession no. AJ006122 XP002191533 abstract ---	4,22,54
A	DATABASE EMBL [Online] 22 September 1998 (1998-09-22) BIASSONI R.: "Homo sapiens mRNA for NK receptor (NKp46), isoform d" retrieved from EBI Database accession no. AJ006123 XP002191534 abstract ---	4,22,54
A	SIVORI SIMONA ET AL: "NKp46 is the major triggering receptor involved in the natural cytotoxicity of fresh or cultured human NK cells. Correlation between surface density of NKp46 and natural cytotoxicity against autologous, allogeneic or xenogeneic target cells." EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 29, no. 5, May 1999 (1999-05), pages 1656-1666, XP001064097 ISSN: 0014-2980 abstract --- -/--	1-3, 8-21,27, 29,31, 33-39, 41-43, 47-51, 53,58-60

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 01/00664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FALCO, MICELA ET AL: "Identification of the rat homologue of the human Nkp46 triggering receptor" IMMUNOL. LETT. (1999), 68(2,3), 411-414, XP001064058	1-3, 8-21,27, 29,31, 33-39, 41-43, 47-51, 53,58-60
	abstract ---	
P,X	MANDELBOIM OFER ET AL: "Recognition of haemagglutinins on virus-infected cells by Nkp46 activates lysis by human NK cells." NATURE (LONDON), vol. 409, no. 6823, 2001, pages 1055-1060, XP002191494 ISSN: 0028-0836 the whole document -----	1-3, 8-21,27, 29,31, 33-35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 01/00664**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 33-34 partially
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: partially 1,8-18, 33-40, 47-51, 58-64, 71-75,
82 and fully 2-4, 19-22, 27, 29, 31, 41-43, 52-54,
65-67, 76-78

A target complex comprising NKp46 , corresponding Nkp46-Ig fusion protein , conjugate ,expression vector , antibodies , pharmaceutical composition , and diagnostic composition .

2. Claims: partially 1,8-18, 33-40, 47-51, 58-64, 71-75,
82 and fully 5-7, 23-26, 28, 30, 32, 44-46, 55-57,
68-70, 79-81

A target complex comprising NKp44 , corresponding Nkp44-Ig fusion protein , conjugate ,expression vector , antibodies , pharmaceutical composition , and diagnostic composition .

3. Claims: partially 1,8-18, 37-39, 51, 58-63, 71-74

A target complex comprising NKp30,corresponding conjugate ,expression vector , antibodies , pharmaceutical composition , and diagnostic composition .

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 75-82 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Although claims 61-74 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 33-34 partially

Present claims 33-34. relate to a product defined by reference to a desirable characteristic or property, namely antibodies that recognize and bind to ligands to the NKp46 or NKp44 receptor .

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products being antibodies that recognize and bind to the hemagglutinin of influenza virus or hemagglutinin-neuraminidase or parainfluenza virus , e.g those prepared in examples 3-7 and mentioned in the description at page 2 paragraph 3 .

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/IL 01/00664

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9636720	A	21-11-1996	CA	2217020 A1		21-11-1996
			EP	0828843 A1		18-03-1998
			JP	11505124 T		18-05-1999
			WO	9636720 A1		21-11-1996

WO 9923867	A	20-05-1999	AU	1389999 A		31-05-1999
			CA	2308440 A1		20-05-1999
			EP	1029049 A2		23-08-2000
			JP	2001522589 T		20-11-2001
			WO	9923867 A2		20-05-1999
			ZA	9810133 A		17-05-1999

WO 9625953	A	29-08-1996	AU	708339 B2		05-08-1999
			AU	4858896 A		11-09-1996
			CA	2209300 A1		29-08-1996
			CZ	9702599 A3		13-05-1998
			EP	0871495 A1		21-10-1998
			FI	973437 A		16-10-1997
			HU	9801873 A2		30-11-1998
			JP	11505409 T		21-05-1999
			NO	973864 A		22-10-1997
			NZ	302513 A		29-11-1999
			RU	2167676 C2		27-05-2001
			WO	9625953 A1		29-08-1996

WO 9626265	A	29-08-1996	US	5912170 A		15-06-1999
			AU	703125 B2		18-03-1999
			AU	4767596 A		11-09-1996
			CA	2209301 A1		29-08-1996
			CZ	9702601 A3		13-05-1998
			EP	0812352 A1		17-12-1997
			FI	973466 A		22-08-1997
			HU	9800459 A2		29-06-1998
			JP	11500621 T		19-01-1999
			NO	973863 A		22-10-1997
			NZ	302090 A		28-01-2000
			WO	9626265 A1		29-08-1996
			ZA	9601476 A		06-03-1997

WO 9509011	A	06-04-1995	AU	702178 B2		18-02-1999
			AU	7924594 A		18-04-1995
			CA	2172393 A1		06-04-1995
			EP	0726779 A1		21-08-1996
			JP	9506073 T		17-06-1997
			WO	9509011 A1		06-04-1995
			US	5641875 A		24-06-1997
			US	5641863 A		24-06-1997
			US	5821071 A		13-10-1998
			US	5776910 A		07-07-1998
			US	6068983 A		30-05-2000
